Health Risk Assessment Research: The OTA Report

The 1950s, a time of placid prosperity, was also an era in which the United States awoke to health threats in its environment. Out of that awakening came a scientific discipline that now, decades later, determines not only how much residual pesticide may safely be allowed in an orange, but also attempts to define how much exposure to carcinogenic chemicals may eventually lead to death from cancer.

Health risk assessment research is based on a multidisciplinary alliance of physics, chemistry, biology, genetics, geology, pharmacology, pathology, and statistics. This alliance, the basis for a whole new field of analysis, grew out of the need for courts, industry, and government to respond to the demands of the public to quantify the potential effects of toxic substances and radiation on human health, as well as to find some way to judge acceptable limits of exposure.

As such, the practice of health risk assessment is only about 20 years old; yet, its methods and principles are widely used in policy decisions that affect millions of lives and involve hundreds of billions of dollars. How far the field has come, how useful it has been in regulating the substances considered dangerous to health or the environment, and how helpful it has been in identifying these substances are all assessed in a report from the Office of Technology Assessment, which will be published in the fall.

In an early draft of its report, the OTA concludes that health risk assessment research is necessary; however, major gaps in its practice and application need to be closed in coming years. Most pressing is the need for more research in environmental health to create, identify, or develop better methods to be used in defining and assessing risk; this is referred to as methodological research.

The second area in which there is room for improvement is policy making. Health risk assessment is now conducted by many scientists in many agencies. The administrators of these agencies must communicate across bureaucratic boundaries to acquire or conduct relevant research and generate the best risk assessments. Similarly, OTA says, government agencies now set their own separate agendas, rarely working together to solve common problems; turf battles are not unknown. Although different federal statutes govern the kinds of risk assessments done by the agencies, therefore limiting some of the administrators' control, the agencies must somehow end their isolation and learn to work together.

Origins of Health Risk Assessment

Opinions differ on how the process of risk assessment began. But it is agreed that the Delaney Amendment to the Food, Drug and Cosmetic Act, enacted in 1958 after Congressman James Delaney's impassioned plea for control of carcinogens in foods, provided the initial impetus. The New York Democrat's wife had just died of cancer, and Delaney wanted to limit the entire population's exposure; thus, the law that bears his name states that any substance shown to be a carcinogen cannot be added to food.

Existing law at the time stated that food and drugs must be safe, and the Food and Drug Administration regulated substances in foods at the level of parts per million. As the science of analytical chemistry advanced in the 1960s and 1970s and detection of chemical at parts per billion or parts per trillion levels became routine, the question became if only one part per quadrillion of a given carcinogen is present in a food substance, such as food coloring, is that reason enough to ban the product? Under the Delaney Amendment, as interpreted by the court, the answer would be yes, and the food substance could not be sold for human consumption. But then, if such a tiny proportion of carcinogen were present, how harmful could it be?

To determine answers to these kinds of questions, scientists developed new methods of predicting adverse effects from low levels of exposure. The first paper on estimating risk from exposure to low doses of substances based on tests in which animals were exposed to high doses was published in 1961. As formal procedures for performing animal bioassays, originally used in qualitative risk assessment, were standardized in the 1960s and 1970s, regulatory agencies began performing risk assessments regularly in the 1970s.

In 1983, a National Research Council committee released *Risk Assessment in the Federal Government: Managing the Process*, which defined the steps in risk assessment and established a generally accepted nomenclature. Since the late 1980s risk assessment has been branching out from its original focus on carcinogens and now evaluates the effects on other systems, such as reproductive toxicity and birth defects arising from exposure to toxins in food and the environment.

On the 10-year anniversary of its first general publication in the field, the National Research Council released a second volume, *Issues in Risk Assessment*, evaluating two risk assessment practices, the use of the maximum tolerated dose in animal assays and the two-stage model of carcinogenesis, with an analysis of ecologic risk assessment. Reports are being prepared on exposure assessment and developmental toxicity.

Impetus for the OTA Report

Two congressional requests are responsible for the OTA study. In 1991, Congressmen John Dingell (D-Michigan), chair of the House Committee on Energy and Commerce, and George Brown (D-California), chair of the House Committee on Science, Space and Technology, asked OTA to prepare a report on government health risk assessment research. Later, in 1992, joined by Robert S. Walker (R-California) and J. Lewis (R-California), Brown requested an examination of EPA's approach to reducing exposure to radon in buildings. "The con-

Risk Assessment: You Have to Speak the Language

Risk—the probability of an adverse health effect as a result of exposure to a hazardous substance.

Risk Assessment—the use of available information to evaluate and estimate exposure to a substance and its consequent adverse health effects. Risk assessment consists of hazard identification, exposure assessment, dose–response assessment, and risk characterization.

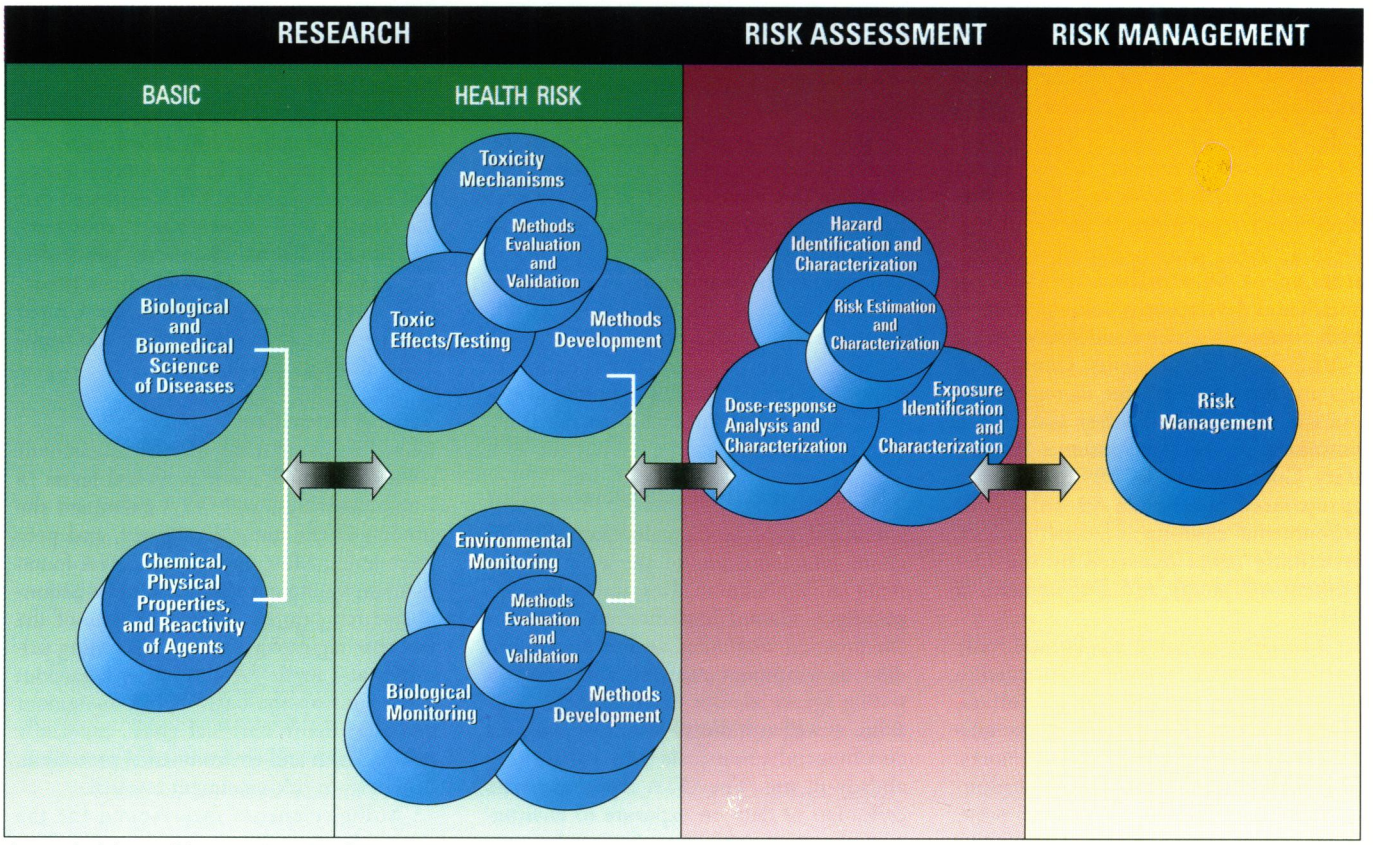
Hazard Identification—the qualitative evaluation of the adverse health effects of a substance(s) in animals or in humans.

Exposure Assessment—the evaluation of the types (routes and media), magnitudes, time, and duration of actual or anticipated exposures and of doses, when known, and, when appropriate, the number of persons who are likely to be exposed.

Dose–Response Assessment—the process of estimating the relation between the dose of a substance(s) and the incidence of an adverse health effect.

Risk Characterization—the process of estimating the probable incidence of an adverse health effect to humans under various conditions of exposure, including a description of the uncertainties involved.

Risk Management—regulatory decision that incorporates information on benefits versus risks of exposure to certain situations.



A new decision-making paradigm. The OTA report suggests a mechanism for linking health risk research to decision-making.

gressional requesters wanted the lay of the land," said Dalton G. Paxman, analyst for the OTA Biological and Behavioral Sciences Program and project director of the report.

In August 1991, as soon as the initial request was received, OTA began assembling a panel of 15 experts from nongovernmental organizations such as universities and those with a particular interest in the field, including industry and environmental groups. OTA staff met three times with the panel over the course of the report's preparation to identify issues and areas of consensus and disagreement. OTA also met individually with agency representatives who provided source materials and other contacts for the investigators. The panel reviewed and revised two drafts of the report before its final edition was agreed upon. In addition, the report was reviewed by more than 100 outside reviewers. OTA also convened 11 other experts, including those from government, for a one-day workshop focusing on research.

Dalton Paxman—There should be a closer link between research and decision-making.

OTA is known for its "report cards" on research activities in and out of government; thus, federal agencies at first expected to be graded individually on their health risk assessment research activities. But as OTA interviewers contacted more and more scientists and administrators within the agencies, another picture emerged.

What the investigators found was that health risk assessment was not just an activity where certain agencies or departments were succeeding and others were failing. There were, rather, problems common to the field throughout government. "The scientists at the agencies felt there were problems, but couldn't put their finger on them exactly," Paxman said. "So now, health risk assessment research is looked at as an integrated federal effort. It's at the integrated overall level where the problems exist, and that's where the opportunities are as well."

Congressional offices had heard that government wasn't using the best risk assessment science, but OTA found that the agencies "are doing good science—but there's more that goes into regulation than science," Paxman said, "There is a link between research and decision-making, and there should be a closer link. But there's a feeling that research would be poisoned by being more closely linked with regulation."

Management has been separated from risk assessment research in government because many believe that managers' expectations could skew the research outcome. Such separation of management and research was supported in the 1983 NAS report. The OTA report states that this gap must now be narrowed to unify risk assessment because, according to Sheila Jasanoff, professor and chair of the Department of Science and Technology Studies at Cornell University, risk assessment is "not a purely scientific activity."

"Indeed," Jasanoff wrote recently in the *EPA Journal,* "risk assessment is often described as an art rather than a science. This formulation emphasizes that risk assessment, like any artistic endeavor, requires the use of subjective judgment."

Impact of Risk Assessment Research

The OTA draft report acknowledges that risk assessment forms the basis of dozens of federal, state, and local laws and regulations, thus influencing the expenditure of hundreds of billions of dollars in health and environmental protection. "Policy makers depend on health risk assessment and research when making regulatory decisions about which risks to tolerate and which to reduce," the report says, pointing out that decisions to reduce risks may lead to vast expenditures for clean-up, while decisions to tolerate those risks may lead to

vast health care and disability costs for those exposed.

The projected cost of complying with EPA regulations in fiscal year 1993, based on data obtained in 1987, is $146 billion to $154 billion. An estimate for the cost of compliance with Food and Drug Administration regulations is not available. However, major pharmaceutical manufacturers spent $9.2 billion in 1991 on research and development, some portion of which represents toxicity and safety testing to satisfy FDA requirements. Compliance costs are also incurred due to regulations from the Occupational Safety and Health Administration and the Consumer Product Safety Commission. In 1992, Congress appropriated more than $9 billion for environmental clean-up at federal facilities, particularly those operated by the Department of Energy and Department of Defense.

"The costs of some environmentally related illnesses are reasonably estimated to reach well into the billions of dollars, although there are no comprehensive estimates available," the OTA report notes. These include lead poisoning, pollution-related acute respiratory conditions, occupational diseases, and certain cancers. The portion of these costs that falls on federal programs such as Medicare, Medicaid, the Veterans Administration, and Social Security is estimated to be about 20% of the total. Yet, OTA says, "private sector costs generally dwarf public expenditures." The private-sector burden for environmentally related illness is about 70%, the report says. Other costs such as human suffering are impossible to value in dollars and cents.

OTA found that health risk assessment research does not typically fit into the sequential four-step process (hazard identification, exposure assessment, dose–response assessment, and risk characterization) outlined by the National Research Council. Instead, OTA classified health risk assessment research into three distinct categories: methodological research, or research to improve the method of risk assessment; basic research that may provide information to improve the foundations of risk assessment; and chemical-specific data development.

OTA characterized methodological research as devising new approaches for extrapolating results from animal models to human estimates of risk and extrapolating from high exposure levels to low exposures, for developing new assay systems, and for measuring uncertainty. This type of research is generic in the sense that its results can have a large impact on many assessments. Moreover, these models are directed at the most uncertain aspects of risk assessments, especially extrapolations from high to low dose, from animal models to humans, and for predicting toxicity of chemicals for which little or no toxicity data exist.

The OTA report separates basic research into two types: basic health risk research and basic sciences. Basic health risk research involves investigating disease mechanisms associated with exposure to toxic agents and examining the experimental tools for use in risk assessment research. Basic biological and biomedical sciences investigate the structure and function of molecules, cells, organs, physiological systems, and their relationship to the functioning organism.

Chemical-specific Data Development

Chemical-specific data development includes the execution of any or all of the steps in the National Research Council's paradigm. Hazard identification represents the broadest and most diverse category of data development research and involves testing agents relevant to the agencies' missions, as well as industry testing of potential commercial chemicals and substances already in use. The OTA report includes collection of data on exposure to environmental agents in this type of research.

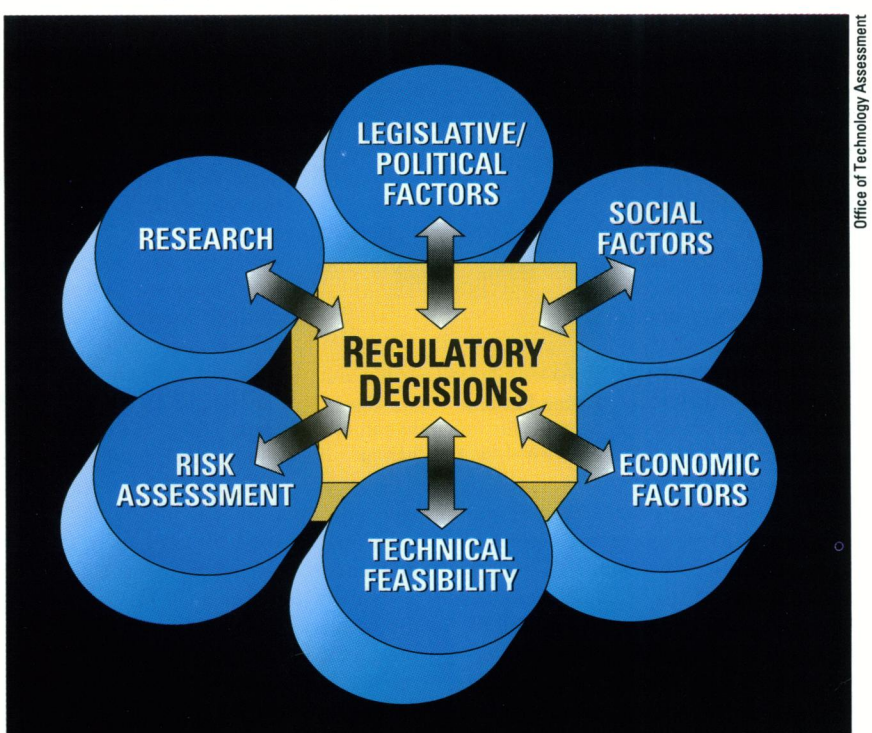
Although some scientists dismiss "data collection" as less important than methodologic or basic research, OTA considers such work to be essential. Attention to accuracy is critical because exposure data and basic toxicologic information usually form the basis of agency rule-making. Data collection provides essential input for both research into risk assessment methods and basic research.

A look at the number of existing chemicals and new compounds added each year explains the need for futher toxicity testing and data development. OTA estimated that the total number of chemicals in commerce including industrial chemicals, pesticides, and food additives—all of which are potentially subject to regulation in the United States—is about 62,000, with an additional 1,500 developed each year.

Setting Priorities

Charting the course of risk assessment research requires work at several levels in federal agencies, and OTA examined the process at the national, agency, and program levels. Most importantly, OTA found that risk assessment research is not a national research priority. This is in spite of the fact that regulatory agencies are setting priorities and levels for cleanup at hazardous waste sites on the basis of risk assessment and that many national goals, especially public health and environmental protection, benefit from risk assessment research.

Some scientists interviewed for the report claim that the research system does not work. Resources, they argue, are squandered on a system that is incapable of setting priorities. Consequently, the perception exists that the areas of highest priority research, i.e., those most likely to improve the process of risk assessment, are not being funded or conducted.



Office of Technology Assessment

Regulatory stew. The OTA report suggests ingredients that should go into regulatory decision-making.

OTA found that no process exists to set national and agency-wide research priorities for risk assessment research; "in fact, on a national level, no priority-setting mechanism appears to be in place for research generally, let alone risk assessment research specifically." "In contrast," said the report, "priority-setting at the program level appears comparatively formalized and well-directed in spite of limited discretionary budgets."

The federal research effort to improve risk assessment is largely decentralized, and though OTA said it observed a few multiagency efforts, participants and nonparticipants displayed little enthusiasm, and some even showed overt hostility toward the effort. Federal scientists conduct research almost entirely in support of their sponsoring agencies and departments, which is also the case for environmental research in general. Risk assessment research is spread across at least 12 different agencies and more than 28 programs. Each agency has its own set of priorities, based on different constituents, legislative mandates, and missions and influenced by historical factors. This makes agency-specific research easier, but it can also make work fragmented and diffuse.

OTA's examination of the resources allocated for research on risk assessment illuminates the breadth of the research. This breadth also contributes to the difficulty in defining health risk assessment research because both the accounting and activities are diffuse and usually overlap with other efforts. OTA estimated the resources for the entire federal effort at between $500 million and $600 million, with less than 20% being devoted to methodological research.

Decision-making

OTA also analyzed the interplay between research and decision-making. At its most basic level, the relationship between research and decision-making can be seen as a feedback loop: half of the loop is the impact of research on decision-making, the other half is the impact of decisions on research that needs to be done. This relationship provides a panoply of options for research priorities. In the current decision-making process, however, research identifies potential dangers, the public conveys its concerns to Congress, and Congress passes laws to address these concerns. According to the report, "This results in a reactive mode that may limit the capacity of agencies, such as EPA, to structure long-term efficient and effective solutions."

OTA admits that there are limits to the capacity of science to inform even on technical issues. "Well beyond more and better science, solving environmental risk assessment problems requires building trust between government, industry and citizens; it requires leadership in setting realistic goals and arranging collaborations of researchers from various disciplines and sectors of society," says the report. The validity of health risk assessments increases with the participation of scientists from many disciplines. Although disciplines such as the physical, biological, toxicological, and biomedical sciences provide the underpinning for assessing health risks, they alone are not sufficient for assessing human risks. Assumptions and policy positions, with embedded value judgments, are necessary to complete risk assessments. The selection of these assumptions would benefit from input from other disciplines, especially those that contribute to the development of laws and regulations. Sheila Jasanoff argues for "bridging the two cultures of risk analysis," which include quantitative sciences and nonquantitative sciences that are humanistic and culturally grounded, such as behavioral and political sciences.

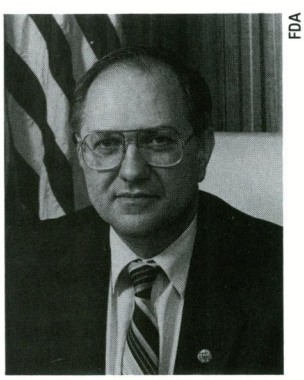
Whatever is expected of it, risk assessment is only one element in formulating regulatory actions. Legislative mandates, social values, technical feasibility, economic factors, and the success or shortcomings of the research that feeds into risk assessment may take a more prominent role than expert predictions of risk. Scientific research can provide a more solid foundation for the decision maker in choosing among alternatives in risk management, but research alone will not necessarily steer decisions to control the most significant risks.

Structuring the Future

"Methods for identifying toxicants, exposed individuals and populations, models for inferring human health effects from animal studies, techniques for estimating risks and predicting health effects with few data are all in need of improvement or development," says the OTA report. To make these improvements, collaboration within and between federal agencies is needed. Such collaboration has taken place between government and universities, but not often between government and industry.

The report provides options for legislative action. The following actions were among those mentioned in the report:

- Continue along the present path, as progress is being made at many agencies toward at least some of the goals the report mentions.
- Launch a national initiative with the White House or executive-level leadership, which would raise the field to a higher level and priority. This would not only attract resources, but promote interagency and extramural cooperation.
- Expand resources available for the field. Given the current fiscal atmosphere, Congress may not increase appropriations for health risk assessment research; therefore, funds could be raised by redirecting budget money already appropriated for other areas. For instance, Congress appropriated $9 billion during fiscal year 1993 to clean up hazardous waste sites at the Department of Energy and the Department of Defense; of that, a small percentage could be set aside for health assessment research to be applied directly to the clean-up effort.
- Institute a system of fees and penalties: users of research could be assessed fees. A percentage of the money sent to the general fund from fines levied by EPA or OSHA could be diverted into a health risk assessment research fund.
- Foster research in risk assessment methodology by establishing a center for health risk assessment methodology research. Alternatively, appoint a central coordinating body to provide leadership in conducting research on risk assessment methodology.
- Encourage technology transfer in developing the field of risk assessment research, by earmarking funds for academic centers on risk assessment research; providing funds to the Department of Commerce to encourage transfer of technology that has commercial applications; encouraging more industry support of health risk assessment research; and by setting aside funds as incentives for collaboration.



FDA

Frank Young—We need to analyze risk assessment assumptions.

Behind the Scenes

The staffers who contributed to the report tried to produce an objective document, and indeed, the tone of the text is measured and its conclusions balanced. Behind the document, however, lie a good deal of passion and opinion.

"I'm a devotee of risk assessment; I do it all the time," said Frank Young, former FDA commissioner. Yet, he acknowledges, "there is a need to analyze the various assumptions that go into the major procedures used in health risk assessment." Young, now director of the Office of Emergency Preparedness/National Defense Medical System, served in the OTA workshop where the report took shape.

One assumption of risk assessment involves laboratory animals such as white mice, which provide a considerable amount of data for risk assessment. The assumption holds that their diet makes no difference in the research outcome.

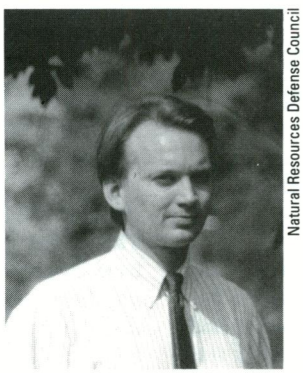
Young disagrees, pointing out that recent work has shown that what laboratory animals eat can have a profound influence on results of risk assessment experiments. This may call into question all previous animal research.

The issue of how to extrapolate animal data to humans remains controversial. One way to clarify that question would be to conduct experiments using substances shown to cause cancer in humans. "No one has undertaken to understand animal responses to known human carcinogens" to see how the responses differ, said James D. Wilson, regulatory affairs director for Monsanto Company and an advisory panel member. "We need to understand that in detail, and we don't."

Environmental Defense Fund

Ellen Silbergeld—Health risk assessment is a waste of time.

There is a need, according to John Vandenberg of the Health Effects Research Laboratory of EPA, to develop better models for testing because "we will never have human models" on which to experiment. Although there has been enormous progress in risk assessment, "no individual should put blind faith in the application of science and human reasoning. Risk assessment is an approximation of truth," says Young.



Natural Resources Defense Council

Erik D. Olsen—Tinkering with risk assessment assumptions is like "readjusting the chairs on the Titanic."

Nevertheless, FDA must perform risk assessment, which includes safety testing, to determine the safety and efficacy of drugs and devices. The regulation and testing of food, though on the surface a simpler task, is as complex as many drug issues. Although the Delaney Amendment prohibits adding carcinogenic substances to foods and food substances, research has since determined that many foods contain natural carcinogens, suggesting that there are factors in diet and human metabolism that protect against these substances. Other foods, sausages and other cured meats, for instance, containing sodium nitrites, are part of certain cultural heritages; thus, they remain on the market. "Some argue that if we were to ban carcinogens altogether, it would be difficult to put together an adequate diet," said Lester Lave, a professor of economics at Carnegie Mellon University who is former president of the Society for Risk Assessment.

Taking a harder line, Ellen Silbergeld of the Environmental Defense Fund calls health risk assessment as a way of dealing with hazards in the environment "a waste of time." To Silbergeld, a substance or a situation is either dangerous or it's not; there is no need to "blur the edges," as she claims risk assessment does. Industry, by demanding more precision, can succeed in postponing regulation. Further, she scoffs at the debate over whether results in animal experiments can be extrapolated to humans, believing a substance harmful to one mammal is likely to be harmful to others, period. "What we should be doing is looking more closely at the distribution of death and disease, and then asking what portion can be prevented," she says, and then making the appropriate policy decisions to make prevention possible. Vandenberg considers such arguments extreme, summing them up as, "If it's bad in humans, don't allow any exposure, or at least limit it. If you're going to limit it, what are you going to limit it to? That's what risk assessment is."

Erik Olson, senior attorney with the Natural Resources Defense Council, says the organization accepts that risk assessment is a part of society, but compares tinkering with risk assessment assumptions to "readjusting the chairs on the Titanic." Olson said, "The way to go is not to figure out whether 20 or 30 people are going to die of cancer from exposure to a substance and try to manage or reduce that risk, but to prevent the pollution in the first place."

Industry has argued, however, that decision makers must take into account everything that's known about health risks, and in many cases "there's more involved than a simplistic policy would admit," Wilson said. Anyone who has ever dealt with government bureaucracy would agree that it is far from simple and, as the OTA report mentions, has been a hindrance to good risk assessment. Scientists contacted tended to agree that, as Vandenberg put it, "within the federal government, you've got Balkanization of policy." However, there may be a reason for that which goes beyond protection of turf. "Agencies are all implementing different pieces of legislation," commented Bryan Hardin of NIOSH. "Each agency tends to have a different set of customers."

Some researchers, including Young and Wilson, point out that risk assessors must keep up with the latest science, and in government, they do not always do so. An example is formaldehyde. High concentrations of this substance cause tumors in rats; it would seem likely, then, that low exposure to formaldehyde among humans would cause enormous numbers of cancers. Yet that, says Wilson, has not happened. Statistical changes were created to make the rat model measure up more accurately to reality, but EPA scientists have been reluctant to modify their standard practice, even though EPA has advised them to do so whenever new information comes along that should be taken into consideration.

Whether the OTA report will result in reform is open to question, but Congress is already taking action in some areas that document mention. Senator Daniel Patrick Moynihan is sponsoring a bill that would set up two advisory committees whose duties would include ranking health and ecology risks, as well as an interagency panel to make federal risk assessment more consistent. It would also establish a research program to improve methodology research (see Spheres of Influence).

The question remains whether this, or any other reforms, will simplify risk assessment or make it more accurate. Some say that the more basic question is whether risk assessments should be used at all, or that the answer is simply to use fewer toxic chemicals. Regardless of the questions asked, it seems clear that in an increasingly hazardous world, the need to inject some measure of certainty into the outcomes of our actions will continue to fuel the drive for risk assessments.

Jan Ziegler

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